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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/746,662	12/22/2000	Lechoslaw Turski	102286-123	1433
23483	7590	07/26/2004		
WILMER CUTLER PICKERING HALE AND DORR LLP 60 STATE STREET BOSTON, MA 02109				
			EXAMINER LI, RUIXIANG	
			ART UNIT 1646	PAPER NUMBER

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/746,662	TURSKI ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Ruixiang Li	1646	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 May 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 21-30 and 38 is/are pending in the application.
- 4a) Of the above claim(s) 26-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21,22,24,25,29,30 and 38 is/are rejected.
- 7) ☒ Claim(s) 23 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>May 3, 2001</u> .   | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### **Status of Application**

The Request filed on April 5, 2004 for Continued Examination (RCE) under 37 CFR 1.114 of Application 09/746,662 is granted. An action on the RCE follows.

### **Applicants' Amendment and Claims**

Applicants' amendment filed on April 5, 2004 has been entered in full. Claims 29 and 38 have been amended. Claims 31-37 have been canceled. Claims 21-30 and 38 are pending. Claims 21-25, 29, 30, and 38 under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

### **Withdrawn Rejections**

The rejection of claims 21, 22, and 24 under 35 U.S.C. 103(a) as being unpatentable over Shishikura et al. (U.S. Patent No.6,133,258) in view of Csuzdi et al. (WO 97/28163) as set forth at pages 3-4 of the final rejection (Paper No. 14, March 6, 2003) has been withdrawn. This rejection is replaced by a new 102(e) rejection (see below).

The rejection of claims 23, 29, 30, and 38 under 35 U.S.C. 103(a) as being unpatentable over Shishikura et al. (U.S. Patent No.6,133,258) in view of Csuzdi et al.

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(WO 97/28163), and further in view of Prineas et al. (Demyelinating Diseases, in Greenfield's Neuropathology, Chapter 13, pages 813-896, 1997), as set forth in the final rejection (Paper No. 14, March 6, 2003), has been withdrawn. The rejection of claims 29, 30, and 38 is replaced with a new 103 (a) rejection, whereas the rejection of claim 23 has been withdrawn in view of Applicants' argument that the prior art does not fairly teach or suggest the method of treating a secondary demyelinating disorder with an inhibitor of the interaction of glutamate with AMPA receptor.

#### **Information Disclosure Statement**

The Information Disclosure Statement originally submitted on May 3, 2001 has been considered in full. A signed copy of Form PTO-1449 is attached to the office action.

#### **Claim Rejections Under 35 U. S. C. § 102 (e)**

Claims 21, 22, and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Shishikura et al. (U.S. Patent No.6,133,258, October 17, 2000; 102(e) date: May 13, 1998).

Shishikura et al. teach a method of treating multiple sclerosis, which is a demyelinating disorder as listed in claim 22, with a non-competitive AMPA receptor antagonist (pyridothiazine derivatives; see, e.g., 3<sup>rd</sup> to 5<sup>th</sup> paragraphs of column 2; claims 7-9), which inhibits the interaction of glutamate with AMPA receptor complex. Thus, the reference of Shishikura et al. meets the limitation of claims 21, 22, and 24.

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**Claim Rejections Under 35 U. S. C. § 103 (a)**

(i) The rejection of claim 25 under 35 U.S.C. 103(a) as being unpatentable over Shishikura et al. (U.S. Patent No.6,133,258, October 17, 2000; 102(e) date: May 13, 1998) in view of Csuzdi et al. (WO 97/28163, August 7, 1997), as set forth in the final rejection (Paper No. 14, March 6, 2003), is maintained.

Applicants submitted a second declaration of Dr. Smith and argue at pages 2-5 of Applicants' response that Shishikura et al. and Csuzdi et al. alone or in combination, do not teach or suggest the claimed methods of treating demyelinating disorders by administering inhibitors of the interaction of glutamate with the AMPA receptor complex. There is no teaching or suggestion in either reference that AMPA receptor antagonists interfere with the process of demyelination, nor is there any enabling disclosure that would provide one of ordinary skill in the art with a reasonable expectation of success in using AMPA receptor antagonists to treat demyelinating disorders as claimed. Applicants submit that the reference of Shishikura et al. describes pyridothiazine derivatives that provide potent inhibition of kainic acid neurotoxicity and anticonvulsant effect against seizure, and therefore are useful as agents for treating neurological disorders, including multiple sclerosis. Applicants further submit that Shishikura et al. do not recognize that multiple sclerosis is a demyelinating disorder, and does not claim usefulness for therapy of such disorders.

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The declaration of Dr. Smith and Applicants' argument have been fully considered, but are not deemed to be persuasive because the reference of Shishikura et al. clearly teaches a method of treating multiple sclerosis with a AMPA receptor antagonist (pyridothiazine derivatives; see, e.g., 3<sup>rd</sup> to 5<sup>th</sup> paragraphs of column 2; claims 7-9) that inhibits the interaction of glutamate with AMPA receptor complex, whereas multiple sclerosis is a demyelinating disorder as listed in claim 22. Thus, the reference of Shishikura et al. alone meets the limitations of claims 21, 22, and 24 (see the new 102(e) rejection), and in combination with the reference of Csuzdi et al. suggest the method of claim 25, regardless whether the cited references teach or suggest that multiple sclerosis is a demyelinating disorder

(ii) Claims 29, 30, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shishikura et al. (U.S. Patent No.6,133,258) as applied to claims 21, 22, and 24 above, and further in view of Prineas et al. (Demyelinating Diseases, in Greenfield's Neuropathology, Chapter 13, pages 813-896, 1997).

Shishikura et al. teach a method of treating multiple sclerosis, which is a demyelinating disorder, with an AMPA receptor antagonist, which is an AMPA receptor inhibitor, as applied to claims 21, 22, and 24 above.

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Shishikura et al. fail to teach a pharmaceutical composition comprising an inhibitor of AMPA receptor in combination with a second agent, e.g., interferon and a method of treating a demyelinating disorder by administering such a pharmaceutical composition.

Prineas et al. teach that interferon- $\beta$  curtails immune activation by counteracting some of the proinflammatory actions of interferon- $\gamma$  and reduces the rate of clinical relapses of multiple sclerosis (3<sup>rd</sup> paragraph, left column of page 857).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to treat multiple sclerosis by administering a pharmaceutical composition comprising an AMPA receptor antagonist taught by Shishikura et al. in combination with interferon- $\beta$  (either simultaneously or separately) with a reasonable expectation of success. One would have been motivated to do so because both an AMPA receptor antagonist and interferon- $\beta$  are beneficial for the treatment of multiple sclerosis and an artisan would reasonably expect the combination of the two compounds to be beneficial for the same purpose, i.e., treating multiple sclerosis.

At pages 5-7 of Applicants' response, Applicants argue that a prima facie case of obviousness has not been established, because the cited references in either alone or in combination do not teach or suggest the treatment of demyelinating disorders by administering an AMPA receptor inhibitor, alone or in combination with another agent. Applicants submit that there would be no motivation to combine the teachings of Shishikura et al. regarding agents for treating neurodegenerative disease with the

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teachings of Prineas, which relate to demyelinating disease. Applicants further submit that, as described in Dr. Smith's declaration, there is no known relationship between the excitotoxicity addressed by Shishikura et al. and cell death due to demyelination and Shishikura et al do not address multiple sclerosis as a demyelinating disorder. Thus, there would be no expectation that any compounds which protect cells against excitotoxicity might be useful in therapy of demyelinating disorders generally.

The declaration of Dr. Smith and Applicants' argument have been fully considered, but are not deemed to be persuasive because the reference of Shishikura et al. teaches a method of treating multiple sclerosis with a AMPA receptor antagonist (pyridothiazine derivatives; see, e.g., 3<sup>rd</sup> to 5<sup>th</sup> paragraphs of column 2; claims 7-9), which is an AMPA receptor inhibitor, whereas the reference of Prineas et al. teaches that interferon- $\beta$  curtails immune activation by counteracting some of the proinflammatory actions of interferon- $\gamma$  and reduces the rate of clinical relapses of multiple sclerosis (3<sup>rd</sup> paragraph, left column of page 857). Thus, it would have been obvious to one having ordinary skill in the art at the time the invention was made to treat multiple sclerosis by administering a pharmaceutical composition comprising an AMPA receptor antagonist taught by Shishikura et al. in combination with interferon- $\beta$  with a reasonable expectation of success. One would have been motivated to do so because both an AMPA receptor antagonist and interferon- $\beta$  are beneficial for the treatment of multiple sclerosis and an artisan would reasonably expect the combination of the two compounds to be beneficial for the same purpose, i.e., treating multiple sclerosis, which is a demyelinating disorder

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listed in claim 22. Accordingly, the reference of Shishikura et al. in combination with the reference of Prineas et al. suggest the invention of claims 29, 30, and 38, regardless whether the cited references address multiple sclerosis as a demyelinating disorder.

### **Objection to Claim 23**

Claim 23 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### **Conclusion**

No claims are allowed.

### **Advisory Information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [Brenda.Brumback@uspto.gov]. All Internet e-mail

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communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Ruixiang Li, Ph.D.  
Examiner  
July 17, 2004

  
**BRENDA BRUMBACK**  
**SUPERVISORY PATENT EXAMINER**  
**TECHNOLOGY CENTER 1600**